

## REMARKS

Claims 1-3 were pending prior to this Response. By the present communication, no claims have been cancelled, claims 4 and 5 have been added, and claims 2 and 3 have been amended to define Applicants' invention with greater particularity. The new claim language adds no new matter, being fully supported by the Specification and original claims. For example, support for new claims 4 and 5 is found in the printed application U.S. 2004/0003757 at paragraph [0029]. Accordingly claims 1-5 are currently pending.

### The Provisional Double Patenting Rejection

Applicants respectfully traverse the provisional rejection of claims 1-3 for alleged obviousness-type double patenting as being unpatentable over claims 1, 3, 6, 7, 10, 13 and 46 of copending Application No. 10/414,582. Submitted herewith is a Terminal Disclaimer disclaiming the terminal part of any patent granted on the subject matter of the above-identified U.S. Patent Application Serial No. 10/607,023, filed June 27, 2003, that would extend beyond the expiration date of any patent that may be granted based on U. S. Patent Application No. 10/414,582 and stating that any patent so granted on this application shall be enforceable only for and during such period that the legal title to the subject matter of said patent shall be the same as the legal title to U. S. Patent Application No. 10/607,023. In view of the Terminal Disclaimer submitted herewith, Applicants submit that copending Application No. 10/414,582 is no longer available as a reference against the present application. Accordingly, reconsideration and withdrawal of the provisional rejection of claims 1-3 under the judicially created doctrine of obviousness-type double patenting are respectfully requested.

### The Rejection under 35 U.S.C. 103(a)

Applicants respectfully traverse the rejection of claims 1-3 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,496,399 to Ison et al. (hereinafter "Ison").

Relying on *In re Best*, the rejection is based on the premise that “where the claimed and prior art products are identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established” (Office Action, page 3). However, Applicants submit that identity in structure or composition and/or substantial identity of the process of production of the composition described in the instant application and in Ison has not been shown.

Before discussing issues of patentability, definitions of “basic” and “acidic” calcium phosphate need to be clarified. A basic calcium phosphate is a calcium phosphate having a Ca/P molar ratio  $> 1.33$  (typically including TCP, TTCP, HA, etc), that, when immersed in water, causes the pH value of the water to rise to  $> 7.0$  (basic). An acidic calcium phosphate is a calcium phosphate having a Ca/P molar ratio  $< 1.33$  (typically including MCP, DCPA, DCPD, etc), that, when immersed in water, causes the pH value of the water to drop to  $< 7.0$  (acidic). Therefore, it is true that the basic or acidic nature of a calcium phosphate depends on pH value of the water. It is also true that the basic or acidic nature of a calcium phosphate depends on the Ca/P ratio of the calcium phosphate.

Accordingly, Applicants disagree with the following assertion of the Examiner: “Both of these calcium phosphates are by composition basic calcium phosphates. The taught dibasic calcium phosphate has a calcium to phosphate ratio of 1.5” (Office Action, 3-4 lines from the bottom of page 2). “Dibasic” means that there are two hydrogen atoms to be replaced by a metal atom. Dibasic calcium phosphate anhydrate (DCPA) has a formula of  $\text{CaHPO}_4 \cdot \text{H}_2\text{O}$  with a Ca/P ratio of 1. Similarly dibasic calcium phosphate dehydrate (DCPD) also has a Ca/P ratio of 1. Regarding the coating on the Ison particles, states: “*The partially neutralized acidic calcium phosphate* which partially coats the basic calcium source particles in the subject cement will be storage stable, i.e. not readily react with the other reactants present in the dry component of the two component cement composition, and *have a calcium to phosphate ratio of at least about 1.0*” (col. 3, lines 60-65; emphasis added). However, the exemplary partially neutralized acidic

calcium phosphates, MCPA, MCPM, DCPA and DCPD all have a Ca/P ratio of 0.5 and 1, thus being “acidic” as taught by Ison.

Applicants also disagree with the Examiner assertion: “The teaching with respect to the phosphates being partially neutralized acidic refers to their pH, not their composition” (Office Action, page 2, bottom). On the contrary, the term “acidic” as used by Ison refers to the “calcium phosphate coating” on the dry component used to make cement, not to the cement. This can be seen from the following statements by Ison: “Alternatively, the dry component may be produced by combining a phosphoric acid solution with a basic calcium source particle slurry under conditions where partially neutralized acidic calcium phosphate precipitates on the surfaces of the basic calcium source particles” (‘339 patent, col. 2, lines 61-66). Thus, according to Ison, acidic precipitates are formed on the surface of the particles, which are only partially neutralized: “Prior to complete neutralization of the acidic phosphate source, the neutralization reaction is stopped through removal of the available water” (‘399 patent, col. 2, lines 51-53). “The proportion of the particle surface that is coated with the partially neutralized acidic calcium phosphate will be dependent on the calcium source particle size, with larger particles having a greater proportion of their surfaces coated with *the acidic calcium phosphate*” (‘399 patent, col. 3, lines 51-55; emphasis added). It is very clear that the acidic calcium phosphate is coated onto particles of basic calcium source as a result of the reaction: “The basic calcium sources which are not to be coated with the *acidic calcium phosphate* will typically be soluble in the aqueous solvent and react with the acidic phosphate source in the partial reaction, e.g. as a neutralizing agent” (‘399 patent, col. 5, lines 26-38). In addition, Ison discloses: “Additional calcium sources may be included in the dispersion which influence the type of *acidic calcium phosphate* that precipitates on the calcium phosphate particles, such as the formation of MCPM over DCPD” (‘399 patent, col. 7, line 65 to col. 8, line 1). Taken together, these statements show that the partially neutralized calcium phosphate coating is acidic with a Ca/P ratio of 0.5 (MCPM) to 1.0 (DCPD) and occurs on the dry particles, not on cement made from the particles.

Thus, Applicants submit that the Examiner erroneously interprets statements in the '399 patent that pertain to dry particles, as being the same "product" as Applicants' cement. For example, the Examiner applies Ison's statement regarding Ca/P ratios in the disclosed "two component cement" as if Ison were describing the composition of only the particles in the cement (i.e., minus the acidic covering). The Examiner asserts "[t]he taught calcium phosphate particles have a calcium to phosphate ratio of 1-2.5, preferably 1.33-2 and a ratio of 1.67 being more preferred" (Office Action, pages 2-3). This statement, which clearly refers to Ison's two component *cement*, the Examiner relies upon as showing ratios that "overlap and fall within the claimed ranges" (Office Action, pages 2-3), which claimed ranges clearly pertain to the composition of only the particles *in* the invention cement and so do not take into account the composition of the basic fine crystals on the surfaces of the particles in the cement.

This misinterpretation provides a basis for the Examiner's application of case law holding that product claims with numerical ranges which overlap prior art ranges are obvious. Applicant submits that particles are not the same "product" as a two component cement.

Moreover, Applicants disagree with the Examiner's assumption that the "coating" and method of its production disclosed by Ison would result or render obvious the claimed "whiskers or fine crystals" formed on the invention calcium phosphate cement. "Coating" according to the dictionary means "thin layer or covering", "a coat or layer over a surface". Applicants respectfully submit that Ison's disclosure regarding an "*acidic* coating" is distinctly different from Applicants' claimed "whiskers or fine crystals of *basic* calcium phosphate" and that Ison's disclosure would not be sufficient to suggest modifications other than those resulting in an acidic coating on a surface of a basic calcium phosphate particle.

Those of skill in the art would not be motivated by Ison to adapt the disclosed particles and cement along the lines of the present invention because Ison's methods are remote from those used in fabrication of the claimed cements. Ison's method of making the partially acidic calcium phosphate coating on the basic calcium phosphate particles disclosed by '399 patent is

characterized by 1) using a relatively smaller amount of acidic phosphate source, e.g. MCPM, and a relatively greater amount of basic calcium phosphate particles; 2) the neutralization reaction of the dissolved acidic phosphate source and the basic calcium phosphate particles; and 3) stopping of the neutralization reaction at a level lower than 50% of the neutralization reaction, preferably no more 20%, more preferably no more 10% (col. 2, lines 46-53; col. 5, lines 38-48; and col. 6, lines 33-38).

By contrast, the process that results in the calcium phosphate cement of the present invention is characterized by 1) inducing the growth of whiskers or fine crystals of basic calcium phosphate on surfaces of calcium phosphate particles with a wetting agent; and controlling the growth of whiskers or fine crystals of basic calcium phosphate. Although both processes use calcium phosphate particles, liquid and a stopping (controlling) step, the process disclosed in the '399 patent a) requires combination of an acidic phosphate source, a sufficient amount of aqueous solution to dissolve the acidic phosphate source, and basic calcium phosphate particles; and b) forming the acidic coating from the neutralization reaction. Thus Ison's process requires formation of an acidic solution for formation of the acidic coating from the neutralization reaction.

In fact, the process of making the invention cement does not necessarily require use of an acidic solution. In Example 16 as shown in Table 2 of the specification of the present application, ethanol was used as the wetting solution in formation of the invention cement. Moreover, as disclosed in a related application, US 2004-0003757 A1, a  $(\text{NH}_4)_2\text{HPO}_4$  solution (a basic solution with pH=8.6) is often used in formation of fine basic crystals on TTCP particles (Examples 1, 6, 7 and 9 in US 2004-0003757 A1). The invention cement can also be made without any phosphate in the solution, for example, HCl solution has been successfully used to form fine basic crystals on TTCP particles (Examples 4 and 5 in US 2004-0003757 A1). In such case, HCl is not involved in any chemical reaction with TTCP. The process of formation of the "covering" on Ison's particles is not "the same" as that used in formation of the fine basic crystals on the particles in the invention calcium phosphate cements.

In view of these differences, Applicants respectfully submit that the process of making an acidic coating on the basic calcium phosphate particles disclosed in '399 patent would neither suggest nor motivate those skilled in the art to make fine crystals of basic calcium phosphate on calcium phosphate particles.

In addition, the properties of the invention cements differ greatly from those in the cited art. In support of this assertion, Applicants submit herewith a Declaration under 35 U.S.C. § 1.132 signed by inventor Dr. Chien-Ping Ju, which describes parallel tests conducted to compare the properties of the calcium phosphate cement (CPC) described in Examples 5, 6, and 7 of the present application with CPCs prepared as described in Examples 1, 4 and 5 of '399 patent (those described in Examples 2 and 3 were not prepared due to lack of some necessary facilities). According to the statements of Dr. Chien-Ping Ju in the Declaration and the data contained in Exhibits 1-4 attached thereto, all of the CPCs prepared according to the descriptions in the '399 patent differed in many aspects from those prepared according to the description in the Specification.

For example, none of the prior art CPC particles had a coating of fine surface crystals of any type. Thus, it seems unlikely that the coverings formed on particles according to Ison's methods are identical or even similar to those required by Applicants' claims.

In addition, a pronounced difference in the properties of the invention and prior art CPCs was revealed (see Exhibits 2-4) by immersing the prior art CPCs in Hank's solution for twenty seconds, a test of competency of the CPCs under physiological conditions as would be encountered during actual use. While the compressive strength of the invention CPC actually increased after soaking in Hank's solution for up to one day, all of the samples of Ison's cements substantially dissolved when immersed in Hank's solution for 20 seconds.

Applicants submit that these differences between the properties of the invention and prior art CPCs rebut the presumption of *In re Best* that the claimed and prior art products are identical

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or substantially identical in structure or composition, or are produced by identical or substantially identical processes. Accordingly, Applicants submit that *prima facie* obviousness is not established over Ison, and reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that all rejections have been overcome and allowance of claims 1-5 is respectfully requested.

If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Declaration under 35 U.S.C. §1.132  
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